The Laryngoscope
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Distinct Histopathology Characteristics in Empty Nose Syndrome

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Objectives/Hypothesis: Empty nose syndrome (ENS) is a controversial disorder and the change of histopathology has never been discussed. This study aimed to conduct a structured histological review to improve the diagnosis and understanding of ENS. Further immunohistochemical staining of transient receptor potential channel melastatin 8 (TRPM8) was performed.

Study Design: A prospective case–control study in a tertiary medical center.

Methods: Consecutive patients with ENS who were diagnosed and received surgical intervention after failure of conservative management were included. Patients with benign pituitary gland tumor receiving transsphenoidal excision were enrolled as control group. Biopsy of inferior turbinate was obtained during surgery for histological review and immunohistochemical staining.

Results: Seventeen patients with ENS and six patients as a control group were established for structured histological review. Patients with ENS presented significantly more squamous metaplasia, a higher rate of submucosal fibrosis, and a lower submucosal gland number grading. Additionally, a unique histological change called goblet cell metaplasia was found in the ENS group. The respiratory epitheliums of ENS were mostly intact with preservation of ciliated cells and goblet cells. The ENS group had a significantly lower expression level of TRPM8.

Conclusions: The nasal mucosa of ENS experienced some airway remodeling and thermoreceptors downregulation, which contribute to clinical symptoms. The distinct histology of ENS included preserved respiratory epithelium and goblet cell metaplasia, accompanying with characteristics similar to atrophic rhinitis. Biopsy of the inferior turbinate may help diagnose ENS.

Key Words: Atrophic rhinitis, empty nose syndrome, histopathology, immunohistochemical stain, TRPM8.

Level of Evidence: 4

***Laryngoscope*, 00:1–5, 2020**

INTRODUCTION

Empty nose syndrome (ENS) remains a poorly recognized but crippling disease for rhinologists and patients. The term ENS was originally described in 1994, addressing the patent airspace on images in patients with partial or total inferior or middle turbinectomy histories.[1] The loss of turbinates may result in mucosal dysfunction, aberrant neurosensory system, and airflow pattern alterations, triggering a specific manifestation in these patients.[1] The main symptom of ENS is the so-called paradoxical nasal obstruction, meaning the patient has a sensation of nasal stuffiness despite the large airspace in the nasal cavities. Other common presentations of ENS include dyspnea, nasal and pharyngeal dryness, hyposmia, rhinorrhea or postnasal drip, nasal crusting, inability to concentrate (aprosexia nasalis), chronic fatigue, frustration, irritability, anger, anxiety, depression, and even hyperventilation syndrome.[1–3]

However, the diagnostic criteria of ENS are not yet established because of the lack of reliable objective measurement. The diagnosis is made upon the combination of past operative history, reported symptoms, physical examination, and image findings. A cotton test is helpful for diagnosing and surgical planning, and a positive result may indicate eligibility for surgical treatment.[2] The common surgical intervention involved a transnasal approach with implant material secured within a submucosal pocket, which aims to reconstruct the nasal airflow and increase airway resistance. It is documented that submucosal reconstruction could improve not only sinonasal but also psychological outcomes[2,4,5] and that lateral wall implantation is preferred for its superior outcome, particularly regarding rhinological symptoms and sleep function.[6]

The pathophysiology of ENS is a puzzling complex with limited evidence available. Previous computational fluid dynamics (CFD) analysis according to virtual turbinectomies in three-dimensional models showed that, except for nasal resistances, nasal heating and humidification efficiencies decreased significantly after both total tubinectomies.[7] Recent image-based CFD studies performed in ENS patients revealed a lower airflow[8] and peak wall shear stress[9] surrounding the inferior turbinates. Additionally, the trigeminal function of the nose measured by menthol lateralization detection thresholds was impaired in these patients.[8–10] These studies showed changes in airflow pattern and trigeminal dysfunction in ENS. However, the sensation of nasal patency is closely related to thermoreceptor-like transient receptor potential channel melastatin 8 (TRPM8) in nasal

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Editor's Note: This Manuscript was accepted for publication on February 4, 2020.

This study was supported by the grants from Chang Gung Memorial Hospital (CMRPG1H0111). The authors have no other funding, financial relationships, or conflicts of interest to disclose.

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DOI: 10.1002/lary.28586

mucosa, which remained to play an implicit role in ENS.[1] Further, histopathological change of ENS has not been addressed in the literature. In this prospective cohort, we would like to interpret the histological change and the presentation of thermoreceptors in the nasal mucosa of patients with ENS. We hope the histological analysis of this first attempt to date may bring more recognition to this complex disease.

MATERIALS AND METHODS

Patients and Study Design

This study was approved by the institutional review board of Chang Gung Memorial Hospital, Taoyuan, Taiwan. Between 2016 and 2017, consecutive patients who were diagnosed and underwent submucosal reconstruction over the lateral wall of the nasal cavity for ENS by the same physician (Dr. Lee) were invited to this study. Patients with benign pituitary gland tumors with neither sinonasal symptoms nor sinonasal disease confirmed by image studies who underwent transsphenoidal surgery were enrolled as the control group for histological analysis. Exclusion criteria included an age of <18 years or the presence of other sinonasal diseases confirmed by endoscopy or images. Written informed consent was obtained from all patients before enrollment. The surgical procedure of submucosal implantation for ENS was described in our previous study.[6]

Diagnosis of ENS and the Cotton Test

The diagnosis for ENS was based on the operative history of middle or inferior turbinectomies resulting in paradoxical nasal obstruction, breathing discomfort, pharyngeal dryness, and other related discomforts. Endoscopy was performed in all patients with ENS to show an excessive loss of turbinates' volume with wide open nasal cavity. Patients with any other sinonasal pathology (eg, rhinosinusitis, nasal valve dysfunction, etc.) were meticulously identified and then excluded. After ENS was diagnosed, the candidates for surgical intervention would receive a cotton test without local anesthesia or decongestant.[2] A cotton ball moistened with isotonic sodium chloride was placed into the widest area of common nasal cavity where previous procedures were performed. The patients were asked to breathe through their nose and report any changes in symptoms for 30 minutes. If there was any improvement in symptoms, the cotton test was positive and the patient was considered a candidate for surgery.

Histological Examination and Structured Review

During the procedure of submucosal implantation or transsphenoidal surgery, all patients received a biopsy on the inferior turbinates before any local injection. The biopsy was performed around the midpoint of the remnant inferior turbinate at the site of the most atrophic portion in ENS group. The biopsy was done at the similar location for the control group. The biopsied tissue was no more than 0.5 cm^3, and consecutive sections (5-μm thickness) of formalin-fixed, paraffin-embedded specimens from all patients were sent to routine hematoxylin and eosin stain. Histological analysis was performed according to the following variables (Table I) including squamous metaplasia (present or absent), submucosal fibrosis (present or absent), chronic lymphocytic infiltration (present or absent), grading of submucosal gland density (from 0 to 4), goblet cell metaplasia (present or absent), and the present or absence of cilia and goblet cell in the epithelial layer.

TABLE I.
Histological Variables Applied in Structured Review.

Variables	Measures of variables
Squamous metaplasia	Present or absent
Submucosal fibrosis	Present or absent
Chronic lymphocytic infiltration	Present or absent
Grading of submucosal gland density	The estimated area percentage occupied by submucosal glands in high power field with the present of mucosa layer 0 = no submucosal gland 1 = 0–25%; 2 = 25–50%; 3 = 50–75%; 4 = 75–100%
Goblet cell metaplasia	Present or absent
Ciliated epithelium	Present or absent
Epithelium with goblet cell	Present or absent

Immunohistochemical Stain and Scoring

The representative specimens that included the intact mucosa and submucosal layers were used for further immunohistochemical (IHC) staining. The sections of qualified specimens were subjected to IHC analysis with the anti-TRPM8 antibody (ab3243; Abcam, Cambridge, UK). The IHC staining was performed via an automatic device and under the manufacturer's instructions (Bond, Vision Biosystems, Mount Waverley, VIC, Australia).

The expression level of the thermoreceptors in the IHC stain was determined by using a combined scoring method that accounted for both the staining intensity and the percentage of stained cells.[11] Visually estimated staining intensities were scored as 3, 2, 1, and 0, which indicated strong, moderate, weak, and negative expressions, respectively. The percentage of cells that stained at the specific level was also calculated at low power field. The percentage of stained cells multiplied by the intensity scores would result in a sum of the expression level, ranging from 0 to 300.

TABLE II.
Demographics Data and Clinical Measurements.

	ENS (n = 17)
Age, mean (SD) (yrs)	48.53 (11.84)
Gender, male:female	13:4
Smoking, n (%)	6 (35%)
Nasal allergy, n (%)	6 (35%)
Asthma, n (%)	2 (12%)
Preop SNOT-25 score, mean (SD)	55.94 (26.43)
Postop SNOT-25 score, mean (SD)	33.29 (21.05)
P value of SNOT-25 change	.006*
Preop BDI-II score, mean (SD)	23.82 (16.88)
Postop BDI-II score, mean (SD)	8.06 (9.97)
P value of BDI-II change	.002*
Preop BAI score, mean (SD)	19.18 (12.07)
Postop BAI score, mean (SD)	8.53 (9.87)
P value of BAI change	.004*

*Statistically significant.

BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory-II; ENS = empty nose syndrome; SD = standard deviation; SNOT-25 = SinoNasal Outcome Test-25.

TABLE III.
Comparison of Histological Results Between ENS and Control Group.

	ENS group (n = 17)	Control group (n = 6)	*P*
Present of squamous metaplasia, n (%)	13 (76%)	1 (17%)	.018*
Submucosal fibrosis, n (%)	16 (94%)	2 (33%)	.008*
Chronic lymphocytic infiltration, n (%)	14 (82%)	4 (67%)	.576
Submucosal glands number grading (0–4), mean (SD)	1.71 (1.13)	3.17 (0.69)	.013*
Goblet cell metaplasia, n (%)	6 (35%)	0 (0%)	.144
Present of ciliated epithelium, n (%)	16 (94%)	6 (100%)	.100
Present of epithelium with goblet cell, n (%)	16 (94%)	6 (100%)	.100
Expression level of TRPM8, mean (SD)	129.68 (56.91)	251.67 (27.94)	<.001*

*Statistically significant.
ENS = empty nose syndrome; SD = standard deviation; TRPM8 = transient receptor potential channel melastatin 8.

Subjective Outcome Measurements

Before the surgical intervention, patients with ENS were asked to complete subjective questionnaires including SinoNasal Outcome Test-25 (SNOT-25), Beck Depression Inventory-II (BDI-II), and Beck Anxiety Inventory (BAI).[12,13] In our previous studies,[5,6,14] we had demonstrated that submucosal implantation is a feasible treatment to improve both sinonasal and psychological outcomes. The SNOT-25 is used to assess the quality of life especially regarding ENS,[2,15] which scored from 0 (no symptoms) to 5 (severe symptoms) for each item. The BDI-II is a 21-item self-administered instrument designed to detect symptoms of depression, in which each item is rated between 0 and 3. Depression is rated by the total score, where a score of 0 to 13 indicates normal, 14 to 19 mild depression, 20 to 28 moderate depression, and 29 to 63 severe depression. Similarly, the BAI is also a 21-item self-administered questionnaire, where each item is answered on a scale from 0 to 3. A final BAI score of 0 to 7 indicates normal, 8 to 15 mild anxiety, 16 to 25 moderate anxiety, and 26 to 63 severe anxiety. The translated and validated versions of the BDI-II and BAI in traditional Chinese were purchased from the Chinese Behavioral Science Corporation in Taiwan.[16] These patients also completed all measurements 1 year after the operation.

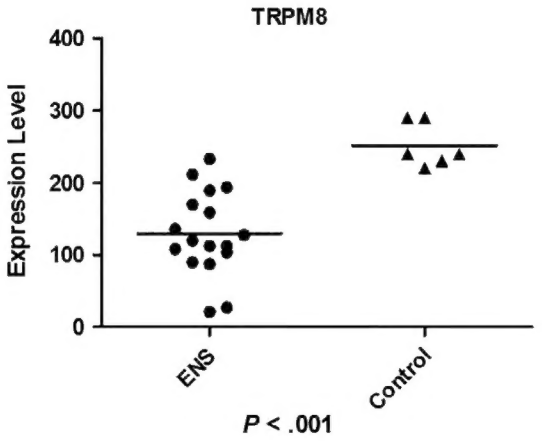

Fig. 2. Expression level of TRPM8 in the two groups. The expression level of TRPM8 was significantly decreased in ENS group (ENS, 129.68 ± 56.91; control, 251.67 ± 27.94, $P < .001$). ENS = empty nose syndrome; TRPM8 = transient receptor potential channel melastatin 8.

Statistical Analysis

The Mann-Whitney *U* test was applied for comparing continuous variables. The two-sided Fisher's exact test was applied for categorical variables between the ENS and control groups. Wilcoxon signed-rank test was used to compare the preoperative and postoperative scores of each item and the total score of the questionnaires. Spearman correlation test was applied to clarify the links between histopathological features and clinical factors. A multivariable logistic regression model was performed to identify the independent factors of ENS. A two-tailed *P*-value of less than .05 was considered to be statistically significant. Statistical analyses were performed using SPSS 16.0 statistical package for Windows (SPSS Inc, Chicago, Illinois, USA).

RESULTS

Demographic Data and Clinical Measurements

A total of 17 patients with ENS who received surgical treatment and completed the 1-year postoperative survey were enrolled in this cohort. The demographic data of ENS group are summarized in Table II. Before surgical treatment, these patients had elevated BDI-II (mean [SD], 23.82 [16.88]) and BAI (mean [SD], 19.18 [12.07]) scoring,

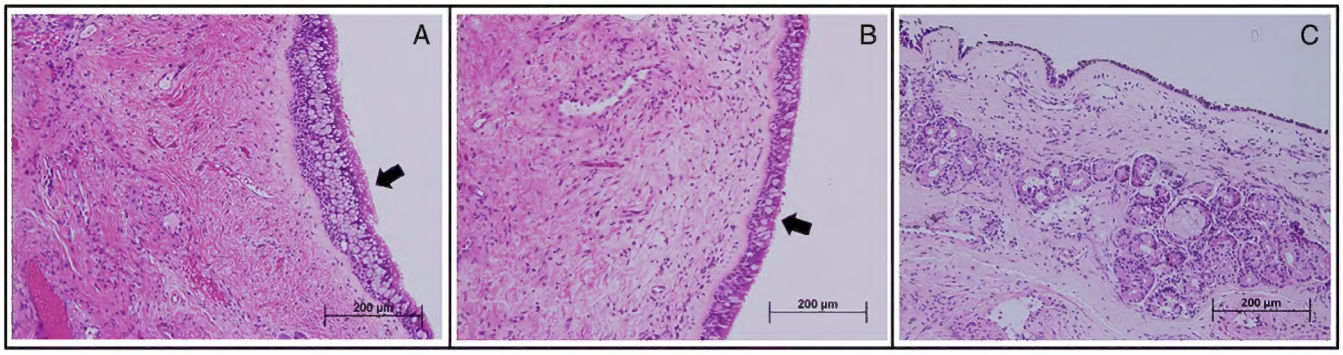

Fig. 1. Typical histological features in hematoxylin and eosin stain for ENS group (A, B) and control group (C). (A) Typical goblet cell metaplasia (arrow), submucosal fibrosis, and glandular atrophy in ENS group. (B) The preservation of goblet cells and cilia on epithelium were identified (arrow) in most specimens from ENS. (C) Abundant submucosal glands with normal ciliated pseudostratified columnar epithelium in control group. ENS = empty nose syndrome. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

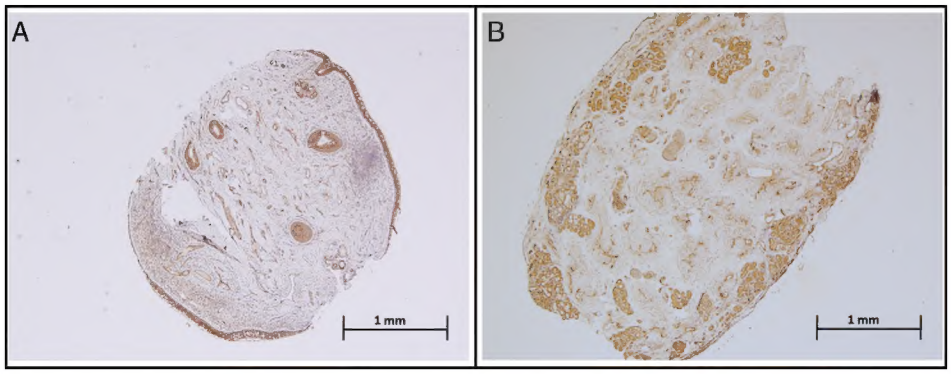

Fig. 3. Representative immunohistochemical stain of TRPM8 in (A) ENS group and (B) control group. The brown signals indicated the positive of TRPM8 receptors which distributed in the nasal cilia, epithelium, and subepithelium around the glands. Note the marked underexpression of TRPM8 in the ENS group. ENS = empty nose syndrome; TRPM8 = transient receptor potential channel melastatin 8. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

indicating a moderate degree of depression and anxiety status. All the subjective measurements regarding rhinological and psychological outcomes showed significant improvements after surgical treatment (Table II).

Histological Results

Six patients were enrolled as control group and the distinct features in histopathology were recorded and graded for patients of both groups (Table III). The typical histological features in hematoxylin and eosin stain of the two groups are showed in Figure 1. Compared with the control group, the ENS group presented more squamous metaplasia (relative risk [RR], 3.54; 95% CI, 1.39–8.96; $P = .018$), more submucosal fibrosis (RR, 11.33; 95% CI, 1.56–82.4; $P = .008$), and a significantly lower submucosal gland number grading (mean [SD], ENS, 1.71 [1.13]; control, 3.17 [0.69]; $P = .013$). Although the difference did not reach a significant level, a unique histological change named goblet cell metaplasia (Fig. 1A) was notably observed in six ENS patients. Epithelial layers from the ENS group were mostly intact with preservation of ciliated cells and goblet cells (Fig. 1B), and there was no significant difference for the presence of cilia or goblet cells between two groups.

Immunohistochemical Study

Further IHC scoring was performed in selected specimens that contained intact mucosal and submucosal layers for more comprehensive analysis. The expression level of TRPM8 was significantly decreased in the ENS group (mean [SD], ENS, 129.68 [56.91]; control, 251.67 [27.94]; $P < .001$; Figs. 2 and 3). The correlation analysis did not identify any association between histopathological features and clinical variables, including age, gender, smoking status, allergy status, and perioperative subjective measurements.

DISCUSSION

ENS remains controversial because the anatomical change cannot explain every presenting symptom. We sought to find out the solutions via histopathology analysis. To the best of our knowledge, this is the first study to address the microscopic changes of ENS. A large series of atrophic rhinitis that reviewed 242 patients with 194 received biopsies revealed that general presentations of atrophic rhinitis were squamous metaplasia with loss of the normal pseudostratified columnar epithelium, loss of cilia and goblet cells, serous and mucous glandular atrophy, diffuse endarteritis obliterans, and chronic inflammatory cells' infiltration.[17] Diagnosis made by symptomatology and confirmed with imaging studies and intranasal biopsy were suggested. Clinically, except differences in past history, atrophic rhinitis presents more fetid odor and mucosal infection with positive bacterial culture, while ENS patients would suffer more dyspnea/suffocation and depression.[18] There was currently no report about distinguishing histological change between these two disease entities.

In this structured review of histopathology in ENS, we found a significantly decreased submucosal glands and more squamous metaplasia and submucosal fibrosis similar to the presentation of atrophic rhinitis. There was no difference in the proportion of chronic inflammatory cell infiltration when compared with the control group. Besides, the ciliated pseudostratified columnar epithelium and mucosal goblet cells were mostly intact in the ENS group. The preservation of respiratory epithelium could result in a relatively healthy epi-immunity in ENS patients and consequently less mucosal infection and infiltration of inflammatory cells. Furthermore, the preservation of respiratory epithelium could also explain the outstanding surgical outcomes in ENS patients. Since submucosal reconstruction may redirect the nasal airflow and reactivate these epitheliums to function properly, surgical treatment could reverse the poor air-mucosal sensations in ENS and result in improvements in rhinological symptoms.[9] However, the submucosal glandular atrophy and fibrosis would still bring the dryness of the nose and the destruction of the mucosal blanket.[17] These histological changes may impair the function of mucosal cooling and consequently induce the nasal dryness and reduce the sensation of airway patency just like atrophic rhinitis.[1]

Goblet cell metaplasia was observed in six (35%) patients with ENS and none in the control group. In asthmatic patients, goblet cell metaplasia represents an airway remodeling and results in more mucus secretions, which become dry sputum occluding the distal airways.[19,20] The

term metaplasia means transdifferentiation from Clara cells or ciliated cells to goblet cells rather than hyperplasia of preexisting goblet cells. Several mechanisms were identified as regulatory pathways of goblet cell metaplasia, including the activated epidermal growth factor receptors (EGFRs) caused by amphiregulin, which was released from damaged epithelial cells.[20] Although there is no literature addressing goblet cell metaplasia in the upper airway epithelium, we postulated that the previous surgical insults for ENS patients may upregulate EGFRs and elicit goblet cell metaplasia. This could result in excessive mucus production and stasis in the nasal airway and limit the evaporation of the mucosal blanket. When the evaporation is reduced, the nasal mucosa would become too warm and subsequently insensitive to airflow triggering a signal similar to dyspnea to the brain.[1] The present study from a microscopic view may help figure out the possible mechanism, rationalize the specific symptoms, confirm the diagnosis, and provide the proper management for ENS patients.

Further IHC staining of TRPM8 receptors revealed a significantly lower presentation in the ENS group. In human nasal mucosa, TRPM8 receptors are mostly present in the nasal cilia, epithelium, and subepithelium around the glands (Fig. 3).[21] The TRPM8 receptor, a trigeminal cool thermoreceptor, could be activated by menthol stimulation and has been implicated in producing the sensation of nasal patency as a response to mucosal cooling.[1,22] Decreased expression of TRPM8 receptors may explain the trigeminal dysfunction and lead to the desensitization of the cooling air and nasal patency in ENS.[8–10] Along with mucosal histological change, the inactivation of TRPM8 receptors caused by impaired mucosal cooling may further worsen the sensation of nasal obstruction in ENS. The perception of nasal patency depends on adequate numbers and stimulations of TRPM8 receptors, which were both declined in patients with ENS. The changes in histology and thermoreceptor expression demonstrated in our cohort indicated that such airway remodeling may be one of the main pathophysiological mechanisms for ENS.

There were several limitations to this research. First, we didn't use the validated diagnostic tool the Empty Nose Syndrome 6-Item Questionnaire (ENS6Q)[23] because it was not available at the time of this cohort started in Jan 2016. However, the mean (SD) of the additional five items specifically for ENS in SNOT-25 was 12.63 (4.86) in our patients with ENS, which was above the cut-off score of ENS6Q. Second, the features of the histological presentation failed to correlate any demographic background or clinical variables, including the subjective measurements. Third, the small sample size may give out a relatively weak statistical significance. The eligible specimen was not easy to acquire from ENS patients or the control group. Fourth, the role of decreased TRPM8 receptors in ENS remains uncertain and deserves further investigation to discover whether it is the leading status in this disease or secondary to the changes in histological features.

CONCLUSION

The histological characteristics of submucosal glandular atrophy, squamous metaplasia, and submucosal fibrosis, as well as the preservation of the cilia and goblet cells in epithelial layers, make ENS complex and unique. Decreased expression of TRPM8 receptors may result in a sensation of nasal obstruction or suffocation. The changes in histology and thermoreceptor expression could be one of the main pathophysiology of ENS. A structured histological study is helpful in understanding and diagnosing ENS.

ACKNOWLEDGMENTS

We would like to thank the research assistant Meng-Chieh Tsai, BS, for data collection and patient contact. This work was supported by the grants from Chang Gung Memorial Hospital (CMRPG1H0111).

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